REMARKS

Claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98, 100-104 are currently pending.

Claims 1, 14, 49, 57 and 98 have been amended to recite that the phosphodiesterase inhibitor is administered before, during or after the training Support for this amendment can be found in the specification at page 12, lines 8-10. Claims 1, 14, 49, 57 and 98 have been rearranged to provide proper internal antecedent basis for the recitation of administration of the inhibitor before, during or after training. Claims 5, 8, 17, 53, 56, 61, 64, 101, 104 have been amended to insert phosphodiesterase inhibitor in place of augmenting agent for proper antecedent basis. Now new matter is added by these amendments.

I. Rejection of claims under 35 U.S.C. 112, first paragraph (enablement)

The Examiner maintains rejection of claims 1, 4-8, 14, 6-20, 49, 51-57, 60-64, 98, 100-104 under 35 U.S.C. 112, first paragraph allegedly "because the specification, while being enabling...for specific phosphodiesterase inhibitors, does not reasonably provide enablement for all phosphodiesterase inhibitors". (Page 3 of the instant Office Action).

When making a rejection on the ground of alleged lack of enablement, the Examiner has the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. In re Wright, supra; In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

The test for enablement entails an analysis of whether one skilled in the art would have been able at the effective filing date to practice the invention using information disclosed in the application and information known in the art without undue or unreasonable experimentation (MPEP § 2164.01; see In re Wands, 858 F.2d 731, 8 USPQ 2d 1400, [Fed. Cir. 1988]). A

finding of lack of enablement and determination that undue experimentation is necessary requires an analysis of a variety of factors (i.e., the In re Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of ordinary skill in the art; 3) guidance provided in the specification; and 4) the state of the prior art. "[H]ow a teaching is set forth, by specific example or broad terminology, is not important"; and furthermore still, "limitations and examples in the specification do not generally limit what is covered by the claims" (MPEP § 2164.08). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. 448 F.2d 872, 878 79; 169 USPQ 759, 762¬ 63 (2d Cir. 197 1), cert. denied, 404 U.S. 10 18, 30 L. Ed. 2d 666, 92 S. Ct. 680 (1972). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. Enzo Biochem., Inc. v. Calgene, Inc., 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting In re Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

Proper application of the legal standard must lead to the conclusion that all claims pending in this application are fully enabled.

The present invention concerns a method of increasing performance gain during treatment of a cognitive deficit associated with a central nervous system disorder or condition in an animal in need of said treatment comprising the steps of:

(a) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task whose deficit is associated with said central nervous system disorder or condition, and

(b) administering to said animal before, during or after training, a phosphodiesterase inhibitor which enhances CREB pathway function;

wherein a performance gain is achieved relative to the performance of said cognitive task achieved by training alone.

The specification teaches that this combination of training with a phosphodiesterase inhibitor can improve the efficiency of existing cognitive training protocols because the combination can reduce the number of training sessions required to yield a performance gain or by requiring shorter or no rest intervals between training sessions to yield a performance gain (see e.g. page 2, line 27 to page 3, line 3).

The Examiner states that the specification fails to provide support for all phosphodiesterase inhibitors. The specification is allegedly limited to only two phosphodiesterase inhibitors, rolipram and iso-buto-metho-xanthine. (Page 5 of the Office Action). The guidance of the specification as to the method of increasing performance gain during treatment of a cognitive deficit associated with a central nervous system disorder by administering all phosphodiesterase inhibitors is allegedly lacking with the exception of rolipram and iso-buto-metho-xanthine.

Applicants respectfully disagree. Various training protocols were known in the art. The specification at page 12, line 14 to page 14, line 7 provides a number of references listing such protocols. Therefore one skilled in the art would be able to conduct the training protocols.

Phosphodiestarease inhibitors are known in the art. The specification provides specific examples of phosphodiesterase inhibitors including rolipram and IBMX (page 18, lines 26-28). One skilled in the art could readily determine whether other phosphodiesterase inhibitors could be employed in the claimed methods.

One skilled in the art could readily test a phosphodiesterase inhibitor to determine whether it resulted in performance gain in training when compared to training in the absence of the phosphodiesterase inhibitor. As the Examiner knows, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation

should proceed. Accordingly, there is adequate information provided in Applicants specification to enable one skilled in the art to perform the claimed invention.

Applicants enclose a declaration by Timothy Tully, PhD. Dr. Tully is one of the inventors of the application. In his declaration, it is his considered scientific opinion that administration of any augmenting agent which enhances CREB pathway function by inhibiting a phosphodiesterase in combination with cognitive training would result in performance gain during treatment of a cognitive deficit associated with central nervous system disorder.

Furthermore, the performance gain during treatment of a cognitive deficit associated with central nervous system disorder can be achieved with any augmenting agent which enhances CREB pathway function by inhibiting a phosphodieterase. Although there are various augmenting agents which may enhance CREB pathway function by inhibiting a phosphodiesterase by a number of different mechanisms, signaling through phosphodiesterase is inhibited, regardless of the manner of inhibition. Thus, the CREB pathway function will be enhanced. Accordingly, ultimately the common mechanism of action of all phosphodiesterase inhibitors is inhibiting the ability of phosphodiesterases to inhibit the CREB pathway function.

Applicants submit that the claims recite a method of increasing performance gain during treatment of a cognitive deficit by administering all phosphodiesterase inhibitors during training. Thus, the claims are not broad in that the claimed subject matter is explicitly recited in the claims and limited to particular methods. Moreover, the specification, and in addition the literature cited therein, teach the method of increasing performance gain during treatment of a cognitive deficit by administering all phosphodiesterase inhibitors. These teachings, examples, methods and techniques enable one of ordinary skill in ways to practice the method of increasing performance gain during treatment of a cognitive deficit by administering all phosphodiesterase inhibitors.

Accordingly, Applicants submit that the claims are enabled and that the rejections of claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98, 100-104 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement are overcome.

II. Rejection of claims under 35 U.S.C. 103(a)

The Examiner maintains rejection of claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98, 100-104 under 35 U.S.C. 103(a) allegedly for "being obvious over Christensen et al., (5,547,979) in view of the Merck Manual. (Page 6 of the instant Office Action).

This rejection is traversed for the following reasons.

As the Examiner is aware there are three requirements to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); M.P.E.P. § 2142; *Cf. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999) Moreover, the prior art must suggest the specific modification that is necessary in order to arrive at the claimed invention. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 934, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990), cert. denied, 498 U.S. 920 (1990).

Second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q. 1016, 1023 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991); *In re Erlich*, 22 U.S.P.Q. 1463, 1466 (Bd. Pat. App. & Int. 1992); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 ("Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure.").

And third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2142.

Applicants submit that the prior art references alone or in combination fail to teach or suggest the claimed invention. The claimed invention is directed to a method of increasing performance

gain during treatment of a cognitive deficit associated with a central nervous system disorder or condition in an animal in need of said treatment comprising the steps of:

(a) training said animal under conditions sufficient to produce an improvement in performance by said animal of a cognitive task whose deficit is associated with said central nervous system disorder or condition, and

(b) administering to said animal before, during or after training, a phosphodiesterase inhibitor which enhances CREB pathway function;

wherein a performance gain is achieved relative to the performance of said cognitive task achieved by training alone

The Examiner agrees that "Christensen et al., fail to disclose multiple training sessions sufficient to produce an improvement in...cognitive task" (Page 6 of the instant Office Action). However, the Examiner asserts that Christensen et al., teaches a method of treating stroke".

Applicants note that Christensen et al., teaches the treatment of the stroke episode by administering an effective 'TNF inhibiting amount" of a compound. Christensen states that the purpose is to inhibit the production of TNF which has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to stroke. Clearly Christensen is contemplating the administration of the rolipram during the acute phase of the stroke episode to treat the tissue injury.

Applicants note that the present application teaches the use of phosphodiesterase inhibitor to enhance CREB pathway function during training which is important in cognitive rehabilition. Christensen does not teach or suggest that the administration of rolipram will result in improved cognitive function. Christensen does not teach phosphodiesterase inhibitors to enhance CREB pathway function. Christensen does not teach or suggest the administration of the phosphodiesterase inhibitors during training. Christensen does not teach or suggest that one could achieve performance gain during training by the administration of phosphodiesterase inhibitors before or during training.

Applicants enclose herewith a reference by Intiso et al., (2003) *Neur. Sci.* 24:390-396 which shows that tumor necrosis factor alpha serum levels increase after stroke, peaking at day 7. Clearly TNF is increased only immediately following ischemic injury. This supports Applicants position that Christensen is simply teaching the administration of rolipram during the acute phase of the stroke to reduce TNF.

The Examiner states that the Merck Manual teaches training of patients suffering from stroke. The Merck Manual does not teach or suggest the administration of phosphodiesterase inhibitors before or during training. The Merck Manual does not does not teach or suggest that one could achieve performance gain during training by the administration of phosphodiesterase inhibitors before or during training.

Applicants enclose publications by Johansson (Stroke 2000:31; 223-230) and Dean (Arch Phys Med Rehabil Vol. 81, April 2000) which indicate that cognitive training for stroke occurs after the acute phase of the stroke and may occur for years after the stroke.

In addition, Applicants have surprisingly found that the administration of a phosphodiesterase inhibitor before, during or after training results in a performance gain by requiring shorter or no rest intervals between training sessions to yield a performance gain.

Accordingly, Applicants maintain that a combination of the cited references does not teach or suggest the claimed invention. Absent a teaching or suggestion in the references either alone or in combination to administer phosphodiesterase inhibitors before or during training, the claimed invention is not rendered obvious. Furthermore, one skilled in the art would not have a reasonable expectation of obtaining a performance gain by the administration of phosphodiesterase inhibitors before or during training as compared to training in the absence of phosphodiesterase inhibitors. In the absence of such a reasonable expectation of success, the invention is non-obvious.

In view of these reasons, withdrawal of this rejection is respectfully requested.

CONCLUSION

The present application is believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited. Please direct any calls in connection with this application to the undersigned at the number provided below.

Please charge any additional fees, including additional fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **43373-0008**.

Respectfully submitted,

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